UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

CENTOCOR ORTHO BIOTECH, INC. AND NEW YORK UNIVERSITY	§	
vs.	§	CASE NO. 2:07-CV-139
ABBOTT LABORATORIES, ABBOTT BIORESEARCH CENTER, INC., AND ABBOTT BIOTECHNOLOGY LTD.	§	

MEMORANDUM OPINION AND ORDER

I. Introduction

In this case, the plaintiffs, Centocor, Inc. and New York University (collectively, "plaintiffs"), contend that the defendants, Abbott Laboratories, Abbott Bioresearch Center, Inc., and Abbott Biotechnology Ltd. (collectively, "defendants"), infringe various claims of United States Patent Nos. 7,070,775 ("the '775 patent") and 7,276,239 ("the '239 patent"). This order addresses the parties' various claim construction disputes. The order will first briefly address the technology at issue in the case and then turn to the merits of the claim construction issues.

II. Background of the Technology

The two patents asserted in this case relate to similar subject matter and relate back to an application, No. 10/198,845 ("the '845 application"), filed in 2002. The '239 patent is a divisional patent of the '845 application and was issued October 2, 2007. The '775 patent was issued July 4, 2006. Both patents claim priority to a series of applications, the earliest of which, No. 07/670,827 ("the '827 application"), was filed in 1991. Both patents are titled "Recombinant A2-Specific TNFα-Specific Antibodies" and share the same written disclosure.[1] These patents are directed to anti-Tumor Necrosis Factor ("TNF") antibodies, fragments, and

[1] All cites to the specification of the '775 patent are to the '239 patent as well.

regions thereof which are specific for human tumor necrosis factor-α ("TNF-α") and are useful in diagnosing and treating a number of TNF-α-mediated pathologies and conditions. *See* '775 patent, Abstract.

TNF-α (cachectin) is a cytokine involved in the regulation of immune cells and is released in the body in response to endotoxins or other stimuli, or antigens. *Id*. at col. 1, ll. 43-45. In healthy humans, the presence of TNF-α has a normal regulatory affect on the immune system. Excessive TNF-α production, however, can lead to inflammation and other symptoms that are associated with auto-immune diseases, such as rheumatoid arthritis, Crohn's disease, and psoriasis. *Id*. at col. 1, l. 60-col. 2, l. 39; col. 6, ll. 45-60. In essence, the overproduced TNF-α acts similar to a toxin and stresses the body. Typically, such stress is caused by a harmful foreign antigen, and the human immune system produces immunoglobulin proteins, or antibodies, that are specific to and neutralize a particular foreign antigen.

Antibodies have a structure universal to all types; they are constructed of two identical heavy chains and two identical light chains of amino acids. Each of the heavy and light chains may be divided into two regions, the constant region and the variable region. The constant region provides a general structure to the antibody, while the variable region provides the specificity of an antibody to a particular antigen. The specificity of an antibody comes from the amino acid chain in its variable region that has specific complementarity to the epitope of an antigen.[2] The portion of the variable region that binds to the antigen is called the complementarity determining region ("CDR").

[2] The patent defines epitope as "that portion of any molecule capable of being recognized by and bound by an antibody at one or more of the [antibody's] antigen binding regions. Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and have specific three dimensional structural characteristics as well as specific charge characteristics." '775 Patent, col. 13, ll. 15-21.

When an invading antigen is a human protein like TNF-α, the immune system does not recognize the TNF-α as a foreign antigen; accordingly, the human body does not have an immune response. The '775 and '239 patents are directed towards a TNF-α antibody that enables the human immune system to neutralize this overproduced protein.

As indicated above, the target protein TNF-α naturally occurs in the human body, and the immune system does not create any antibodies against it. Consequently, the creation of an antibody specific to TNF-α typically requires artificial engineering. Inherent with the engineering of TNF-α specific antibodies, however, is a problem of immune response or immunogenicity issues—the antibodies must be specific to TNF-α, yet must also not invite an immune response themselves. Accordingly, scientists have attempted to engineer antibodies with varying combinations of human and nonhuman materials. *See* '775 patent, col. 2, l. 40-col. 3, l. 55. As mice produce antibodies specific to human TNF-α, mice are the typical species used in such genetic engineering. *Id*. The patents-in-suit specifically discuss a special antibody, designated A2, which has especially potent TNF-α inhibiting activity. '775 Patent, col. 43, ll. 35-41.

Claims 1 and 2 of the '775 patent are exemplary and contain many of the terms at issue in this case.

> 1. An isolated recombinant anti-TNF-α antibody or antigen-binding fragment thereof, said antibody comprising a human constant region, wherein said antibody or antigen binding fragment (i) competitively inhibits binding of A2 (ATCC Accession No. PTA-7045) to human TNF-α, and (ii) binds to a neutralizing epitope of human TNF-α in vivo with an affinity of at least $1x10^8$ liter/mole, measured as an 40 association constant (Ka), as determined by Scatchard analysis.
>
> 2. The antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen-binding fragment comprises a human constant region and a human variable region. '775 Patent, cls. 1 & 2 (emphasis added).

One of the antibodies claimed in the patents is Centocor's biologic treatment Remicade® (infliximab), which contains the novel cA2 antibody and is used to treat rheumatoid arthritis, Crohn's disease, psoriasis, and ankylosing spondilitis. *See* Pl.'s Opening Claim Construction Brief at 4. The defendants make and sell Humira® (adalimumab), which is the accused product and a biologic treatment for rheumatoid arthritis and other autoimmune diseases. *See* Defs.' Opening Claim Construction Brief at 4.

III. Discussion

A. General Principles Governing Claim Construction

"A claim in a patent provides the metes and bounds of the right which the patent confers on the patentee to exclude others from making, using or selling the protected invention." *Burke, Inc. v. Bruno Indep. Living Aids, Inc.*, 183 F.3d 1334, 1340 (Fed. Cir. 1999). Claim construction is an issue of law for the court to decide. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 970-71 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996).

To ascertain the meaning of claims, the court looks to three primary sources: the claims, the specification, and the prosecution history. *Markman*, 52 F.3d at 979. Under the patent law, the specification must contain a written description of the invention that enables one of ordinary skill in the art to make and use the invention. A patent's claims must be read in view of the specification of which they are a part. *Id.* For claim construction purposes, the description may act as a sort of dictionary, which explains the invention and may define terms used in the claims. *Id.* "One purpose for examining the specification is to determine if the patentee has limited the scope of the claims." *Watts v. XL Sys., Inc.*, 232 F.3d 877, 882 (Fed. Cir. 2000).

Nonetheless, it is the function of the claims, not the specification, to set forth the limits of the patentee's claims. Otherwise, there would be no need for claims. *SRI Int'l v. Matsushita*

Elec. Corp., 775 F.2d 1107, 1121 (Fed. Cir. 1985) (en banc). The patentee is free to be his own lexicographer, but any special definition given to a word must be clearly set forth in the specification. *Intellicall, Inc. v. Phonometrics*, 952 F.2d 1384, 1388 (Fed. Cir. 1992). And, although the specification may indicate that certain embodiments are preferred, particular embodiments appearing in the specification will not be read into the claims when the claim language is broader than the embodiments. *Electro Med. Sys., S.A. v. Cooper Life Scis., Inc.*, 34 F.3d 1048, 1054 (Fed. Cir. 1994).

This court's claim construction decision must be informed by the Federal Circuit's decision in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005)(en banc). In *Phillips*, the court set forth several guideposts that courts should follow when construing claims. In particular, the court reiterated that "the *claims* of a patent define the invention to which the patentee is entitled the right to exclude." *Id.* at 1312 (emphasis added)(quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1115 (Fed. Cir. 2004)). To that end, the words used in a claim are generally given their ordinary and customary meaning. *Id.* The ordinary and customary meaning of a claim term "is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Id.* at 1313. This principle of patent law flows naturally from the recognition that inventors are usually persons who are skilled in the field of the invention. The patent is addressed to and intended to be read by others skilled in the particular art. *Id.*

The primacy of claim terms notwithstanding, *Phillips* made clear that "the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the

specification." *Id.* Although the claims themselves may provide guidance as to the meaning of particular terms, those terms are part of "a fully integrated written instrument." *Id.* at 1315 (quoting *Markman*, 52 F.3d at 978). Thus, the *Phillips* court emphasized the specification as being the primary basis for construing the claims. *Id.* at 1314-17. As the Supreme Court stated long ago, "in case of doubt or ambiguity it is proper in all cases to refer back to the descriptive portions of the specification to aid in solving the doubt or in ascertaining the true intent and meaning of the language employed in the claims." *Bates v. Coe*, 98 U.S. 31, 38 (1878). In addressing the role of the specification, the *Phillips* court quoted with approval its earlier observations from *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998):

> Ultimately, the interpretation to be given a term can only be determined and confirmed with a full understanding of what the inventors actually invented and intended to envelop with the claim. The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction.

Consequently, *Phillips* emphasized the important role the specification plays in the claim construction process.

The prosecution history also continues to play an important role in claim interpretation. The prosecution history helps to demonstrate how the inventor and the PTO understood the patent. *Phillips*, 415 F.3d at 1317. Because the file history, however, "represents an ongoing negotiation between the PTO and the applicant," it may lack the clarity of the specification and thus be less useful in claim construction proceedings. *Id.* Nevertheless, the prosecution history is intrinsic evidence. That evidence is relevant to the determination of how the inventor understood the invention and whether the inventor limited the invention during prosecution by narrowing the scope of the claims.

Phillips rejected any claim construction approach that sacrificed the intrinsic record in favor of extrinsic evidence, such as dictionary definitions or expert testimony. The *en banc* court condemned the suggestion made by *Tex. Digital Sys., Inc. v. Telegenix, Inc.*, 308 F.3d 1193 (Fed. Cir. 2002), that a court should discern the ordinary meaning of the claim terms (through dictionaries or otherwise) before resorting to the specification for certain limited purposes. *Id*. at 1319-24. The approach suggested by *Tex. Digital*–the assignment of a limited role to the specification–was rejected as inconsistent with decisions holding the specification to be the best guide to the meaning of a disputed term. *Id.* at 1320-21. According to *Phillips*, reliance on dictionary definitions at the expense of the specification had the effect of "focus[ing] the inquiry on the abstract meaning of words rather than on the meaning of the claim terms within the context of the patent." *Id*. at 1321. *Phillips* emphasized that the patent system is based on the proposition that the claims cover only the invented subject matter. *Id*. What is described in the claims flows from the statutory requirement imposed on the patentee to describe and particularly claim what he or she has invented. *Id.* The definitions found in dictionaries, however, often flow from the editors' objective of assembling all of the possible definitions for a word. *Id.* at 1321-22.

Phillips does not preclude all uses of dictionaries in claim construction proceedings. Instead, the court assigned dictionaries a role subordinate to the intrinsic record. In doing so, the court emphasized that claim construction issues are not resolved by any magic formula. The court did not impose any particular sequence of steps for a court to follow when it considers disputed claim language. *Id*. at 1323-25. Rather, *Phillips* held that a court must attach the appropriate weight to the intrinsic sources offered in support of a proposed claim construction, bearing in mind the general rule that the claims measure the scope of the patent grant.

While the disputed claim terms appear in multiple asserted claims, the parties agree that each term should be consistently construed in every claim term in which it appears. The court now turns to a discussion of the disputed claim terms.

B. "human variable region"; "human light chain"; "human heavy chain"

Claim term, phrase or clause	Centocor's Proposed Construction	Defendants' Proposed Construction
"anti-TNF-α antibody"	"An immunological protein that binds to TNF-α"	"A murine or chimeric antibody (combining DNA sequences from different species) that binds to human TNFα"
"human variable region"	"A variable region that is encoded by a gene derived from human DNA"	"An antibody variable region (V_H and V_L gene products) that has an amino acid sequence predominantly derived from human genetic sequences with complementarity determining regions (CDRs) grafted from a rodent or other non-human species."
"human light chain"	"Light chain encoded by a gene derived from human DNA"	"An antibody light chain (C_L and V_L gene products) that has an amino acid sequence predominantly derived from human genetic sequences with complementarity determining regions (CDRs) grafted from a rodent or other non-human species."
"human heavy chain"	"Heavy chain encoded by a gene derived from human DNA"	"An antibody heavy chain (C_H and V_H gene products) that has an amino acid sequence predominantly derived from human genetic sequences with complementarity determining regions (CDRs) grafted from a rodent or other non-human species."

Within the '775 patent, the term "anti-TNF-α antibody" appears in independent claims 1 and 13 and dependent claims 4, 5, and 6. Within the '239 patent, the term appears in independent claims 3 and 9 and dependent claims 10-16. The term "human variable region" appears in dependent claims 2 and 14 of the '775 patent. The terms "human light chain" and "human heavy chain" appear in claims 3 and 15 of the '775 patent.

The fundamental dispute regarding the above terms is whether the '775 and '239 patents claim an anti-TNF-α antibody that is wholly encoded by a gene derived from human DNA. The defendants argue that the patents-in-suit claim chimeric antibodies, i.e., antibodies that are not

fully human. In support, they point to disclosures in the '827 application and the specification.[3] In relying heavily on the application to the '775 patent, the defendants argue that the patentee discloses a single embodiment and criticizes (or disavows) a human antibody, which, when read together, restrict the patent to a chimeric antibody. Essentially, the defendants are asking the court to limit all instances of "anti-TNF-α antibody" and "human," with the exception of its use in modifying "constant," to a chimeric antibody or something less than fully human, respectively.

As a threshold matter, in light of the defendants' argument, it is necessary to analyze the cases which arguably support such limiting constructions. The defendants focus primarily on three cases: *Astrazeneca*, *Honeywell*, and *Kinetic Concepts*. *Astrazeneca AB, et al. v. Mut. Pharm. Co.*, 384 F.3d 1333 (Fed. Cir. 2004); *Honeywell Int'l, Inc., et al. v. ITT Indus., Inc.*, 452 F.3d 1312 (Fed. Cir. 2006); *Kinetic Concepts, Inc. v. Blue Sky Medical Group, Inc.*, 554 F.3d 1010 (Fed. Cir. 2009).

In *Astrazeneca*, the Federal Circuit reversed the district court's claim construction for not limiting "solubilizer" as recognized by the patent's specification and prosecution history. *Astrazeneca*, 384 F.3d 1333, 1335. In its analysis, the Federal Circuit first looked to the specification, specifically, a passage that strongly indicated the patentee's intention to define the term. *Id*. at 1338-39. Although the court rejected a formalistic approach to its search for a lexicographical statement, it found clear intent in the patentee's statement that, "[t]he solubilizers suitable according to the invention *are defined* below." *Id*. at 1340. The court then looked for indications of disavowal. Indeed, the court found disavowal in both the patent's discussion of certain features of a "solubilizer" and the patent's subsequent criticisms of other features. *Id*.

[3] As the defendants correctly assert, the patent instructs the court to read previous applications as incorporated by reference to the present specification of the '775 patent.

The court counseled against rigid formalism and stated, "[w]here the general summary or description of the invention describes a feature of the invention [] and criticizes other products [] that lack that same feature, this operates as a clear disavowal of these other products (and processes using these products)." *Id*. Finally, the court looked to the patentee's choice of preferred embodiment. The court found further support for disavowal in the patent's consistent use and reference to the limited construction, particularly, references to preferred or "especially preferred" embodiments.[4] The Federal Circuit concluded its analysis by addressing the prosecution history of the patent-in-suit. As it did with the lexicography above, the court cited an instance in the prosecution history in which the patentee referenced a "definition in the specification," finding that "[t]he applicants' characterization of this sentence in the specification as a 'definition' confirms that that the applicants acted as their own lexicographers to redefine 'solubilizer' differently from its ordinary meaning." *Id*.

Faced with a similar issue in *Honeywell*, the Federal Circuit agreed with the district court's limiting construction of "fuel injection system component" and disagreed with its broad construction of "electrically conductive fibers." *Honeywell*, 452 F.3d at 1318. Essentially, the court found implicit definitional support for the first term and implicit disavowal of scope for the second term. Citing usage by the patentee of phrases like "this invention" or "the present invention," the Federal Circuit found a number of instances of language within the specification that led to the conclusion that "a fuel filter is the only 'fuel injection system component' that the claims cover, and that a fuel filter was not merely discussed as a preferred embodiment." *Id*. Regarding the second term, much like in *Astrazeneca*, the court found disavowal of scope through the patent's discussion of the consequences of using an alternative material; "its repeated

[4] The court further noted, "[t]he fact that all of the solubilizers listed in the specification and used in the working examples were surfactants adds further support to the conclusion that the term 'solubilizer' in the claims should be limited, according to the definition employed in the specification, to surfactants." *Id*. at 1341.

derogatory statements concerning one type of material are the equivalent of disavowal of that subject matter from the scope of the patent's claims." *Id*. at 1320.

Finally, although *Kinetic Concepts* addressed a number of issues on appeal, the one pertinent to the present inquiry concerned whether the term "wound" should be limited to a narrow construction, supported by the intrinsic record, or a broad construction, supported by extrinsic evidence. *Kinetic Concepts*, 554 F.3d 1010. As a starting point, the court noted that all of the examples described in the specification pointed toward a limited construction. Furthermore, the court could not find any support for the expanded scope of the construction of "wound."

> [I]n the absence of something in the written description and/or prosecution history to provide explicit or implicit notice to the public—i.e., those of ordinary skill in the art—that the inventor intended a disputed term to cover more than the ordinary and customary meaning revealed by the content of the intrinsic record, it is improper to read the term to encompass a broader definition simply because it may be found in a dictionary, treatise, or other extrinsic source." *Id*. (citing *Nystrom v. TREX Co.*, 424 F.3d 1136, 1145 (Fed. Cir. 2005)).

Against this legal backdrop, the court will now examine the disputed terms and the '775 patent.

Turning to the specification, the great portion of the defendants' argument attempts to convince the court that "human antibody," in the context of the patent and to one of ordinary skill in the art, means something other than fully human. A persuasive portion of the specification, not coincidentally the portion which the defendants contend is "new matter," states as follows:

> Anti-TNF antibodies (Abs) are intended to include at least one of monoclonal rodent-human chimeric antibodies, rodent antibodies, human antibodies or any portions thereof, having at least one antigen binding region of an immunoglobin variable region, which antibody binds TNF. '775 Patent, col. 5, ll. 55-59 (emphasis added).

This portion of the specification favors the plaintiffs' construction.[5] While the defendants argue that the above passage does not define "human antibody," neither does it disclaim a fully human antibody. As indicated above, the balance of the defendants' argument focuses on interpreting what the patentee intended a "human antibody" to mean.[6]

Absent within the specification, unlike in *Astrazeneca*, is an intention to define the term contrary to ordinary usage. In examining the various applications to the '775 patent and the specification itself, the court cannot find express definitional language regarding the term "human" or "human antibody." Although *Astrazeneca* teaches against a rigid definitional approach, the court was able to find clear instances of definitional language—definitional language absent from the '775 specification and incorporated applications.

Turning next to a search for implicit definitions, regarding the '827 application, the isolated portion of the "Description of the Background Art" does not indicate that the invention does not include fully human antibodies. The cited portion does discuss some drawbacks to the use of "human m-Ab-producing cell lines;" however, it does not disclaim any claim scope. In fact, the cited passage appears to discuss some drawbacks to "human m-Ab-producing cell lines" in the context of the mass production of certain human antibodies isolated from human cells that have been immortalized by infection with the Epstein Barr virus. *See* '827 Application (Ex. 5 of Defs.' Opening Claim Construction Brief) at 9. Additionally, as argued by the plaintiffs, in subsequent passages of the '827 application, the patentee describes a solution to the above-cited

[5] The defendants' also suggest that, because the patentee introduced "new matter" in 1992 and 1994 after the first application was filed in 1991, the court should now ignore this and other portions of the specification. This argument is inapplicable for the purposes of claim construction. Several district courts have held that "determining whether a patentee introduced new matter during prosecution is not appropriate during claim construction." *See Biax Corp. v. Intel Corp.*, No. 2:05-CV-184 (E.D. Tex. 2007) (internal citations omitted).

[6] Centocor argues that the defendants focus too heavily on the meaning of "human antibody" and not the meaning of the term in dispute, "human." While such a complaint has merit, as Centocor is not asserting a claim which claims "human antibodies," persuading the court that "human antibody" means something other than fully human will necessarily entail convincing the court that "human" means something other than fully human.

issue. *See id*. at 23; *see also* '775 Patent, col. 14, l. 64-col. 15, l. 9 (discussing the similar solution). Finally, although the '827 application may arguably address the problems associated with human antibodies, the '827 application also includes passages detailing problems associated with murine antibodies. Specifically, in one passage, the '827 application notes that, "due to their murine origin, they are foreign products in humans, induce anti-murine immune responses and tend to be cleared more rapidly from the circulation." *See* '827 Application (Ex. 5 of Defs.' Opening Claim Construction Brief) at 8-9 ("mouse antibodies may not interact as effectively as human antibodies with human effector cells.").

Other portions of the specification cited by the parties generally fall into two categories—those that discuss "human-human," and those that discuss "human constant regions."[7] The defendants' argument regarding the first category is fairly persuasive. '775 Patent, col. 12, ll. 28-30; col. 16, ll. 27-33; col. 19, l 60-col. 20, l. 2. The specification defines "human-human" as a chimeric antibody, which in turn is defined as being derived from a different animal species. *See* '775 Patent, col. 20, ll. 45-54 ("[a] chimeric antibody, such as a mouse-human or human-human . . . ."; *id*. at col. 10, l. 64-col. 11, l. 4 ("[c]himeric antibodies are molecules different portions of which are derived from different animal species . . . .") (emphasis added). The defendants' argument regarding the second category, however, would require inconsistent interpretations of the term "human." '775 Patent, col. 19, ll. 1-8; col. 19, ll. 17-27. The defendants do not dispute that when the term "human" is used to define the constant region, it means "human." *See* Defs.' Opening Claim Construction Brief at 19. When the term "human"

[7] The defendants also cite to portions of the specification which describe "the present invention," and "this invention" for support of their contention that the patent discloses only chimeric antibodies, citing *Anderson Corp. v. Fiber Composites, LLC*. In *Anderson*, however, the Federal Circuit limited the claims to a particular embodiment in pellet or extrudate form because the patent stated that extruding the composite in pellet or linear extrudate form was "required." *Anderson Corp. v. Fiber Composites, LLC*, 474 F.3d 1361, 1367 (Fed. Cir. 2007). The '775 patent does not use such restrictive terms. Furthermore, unlike in *Honeywell*, the '775 patent specification neither contains persuasive implicit definitional support nor disavowal of scope. *Honeywell*, 452 F.3d at 1318-19.

is used to define the above terms, however, the defendants seek to impose a different meaning of "human." Such an argument would violate the principle that a claim term should be construed consistently throughout the claim.

In construing the above terms, the court is not persuaded that the patentee either expressly or implicitly disavowed any interpretation of "anti-TNF-α antibody" or "human" that would encompass a fully human antibody. Absent from the '775 specification is any language expressly limiting scope. Also absent is any implicit recognition of a limiting construction; the '827 application discusses drawbacks to antibodies comprising murine components as well as to antibodies comprising human elements. The patentee has not given the term "human" the strained meaning now proposed by the defendants, and there is no implicit definition of the term "human" to mean "predominantly human but must include non-human parts." In light of the claim language, read in the context of the specification, the court simply cannot find any instances within the specification which call for a limiting construction. In light of the general claim construction premise that claims should not be limited to the preferred embodiment, the court is not willing to limit the above terms as the defendants suggest.

Accordingly, the court defines the disputed terms as follows.

The court defines "anti-TNF-α antibody" as **"an immunoglobulin protein that binds to TNF-α."**

The court defines "human variable region" as **"a variable region that is encoded by a gene derived from human DNA."**

The court defines "human light chain" as **"light chain encoded by a gene derived from human DNA."**

The court defines "human heavy chain" as **"heavy chain encoded by a gene derived from human DNA."**

C. "competitively inhibits binding of A2 (ATCC Accession No. PTA-7045) to human TNF-α"

Claim term, phrase or clause	Centocor's Proposed Construction	Defendants' Proposed Construction
"competitively inhibits binding of A2 (ATCC Accession No. PTA-7045) to human TNF-α"	"Competes with A2 (ATCC Accession No. PTA-7045) for binding to human TNF-α"	"ATCC PTA-7045 is a hybridoma deposited with the American Type Culture Collection. The product of the ATCC PTA-7045 includes the A2 antibody, which binds to human TNFα. An antibody 'competitively inhibits' A2 if, in a standard ELISA or equivalent assay: (i) the antibody blocks binding of the antibody product of ATCC PTA-7045 to human TNFα at least as well as the hybridoma product blocks itself; AND (ii) the blocking of the ATCC PTA-7045 product is due to the test antibody binding the same epitope of TNF-α as the antibody product of ATCC PTA-7045. An 'epitope' consists of amino acid residues on the antigen to which an antibody binds."

Within the '775 patent, the above phrase appears in independent claims 1 and 13 and dependent claims 4, 5, and 6. Within the '239 patent, the term appears in independent claim 9 and dependent claims 10-16.

In defining the above phrase, the defendants propose a construction that addresses "competitively" and "inhibits" separately. In defining "competitively," the defendants seek to require the A2 murine monoclonal antibody and the disclosed anti-TNF-α antibody to compete for the same epitope. In defining "inhibits," the defendants seek to require a definite quantitative level of inhibition.

1. "competitively"

Regarding "competitively," the defendants rely on the specification and the prosecution history for support. The specification's only specific example of competitive inhibition testing occurs between A2, the murine antibody, and cA2, an embodiment of the patent; the test

involves a competition assay in which A2 and cA2 bind to the same epitope. *See* '775 Patent, col. 48, l. 58-col. 49, l. 67. Contrary to the defendants' assertion, however, the specification also allows for competitive inhibition between A2 and other "antibod[ies] having *substantially the same* specific binding characteristics." *Id*. at col. 12, ll. 4-8. Whether or not the experts agree on what a "similar epitope" is, the above cited passage implicitly allows for something more than a competition between A2 and an anti-TNF-α antibody for the *same epitope*.[8] Both the Harlow Laboratory Manual, incorporated by reference in the patents, and the prosecution history also teach against such a limitation. The manual states, "if the sites of interaction are identical *or overlapping*, the unlabeled antibody will compete." '775 Patent, col. 10, ll. 52-57; *see* ED HARLOW & DAVID LANE, ANTIBODIES: A LABORATORY MANUAL 567 (Cold Spring Harbor Laboratory 1988) (Ex. 17 to Pl.'s Reply Claim Construction Brief). Within the prosecution history, in response to an obviousness rejection, the patentee stated, "[t]hus, the claimed monoclonal antibodies, in their ability to inhibit A2 binding, must also bind to the same *or similar* epitope." U.S. Patent Application No. 08/192,093 ("the '093 application") at 7 (Ex. 17 to Defs.' Opening Claim Construction Brief). Accordingly, the weight of the support in both the specification and the prosecution history guides the court away from strictly defining the term as requiring competition for the *same* epitope. Contrary to the defendants' arguments, "overlapping," "similar," and "substantially the same" do not denote two epitopes that are identical.

2. "inhibits"

Regarding "inhibits," the defendants argue that without a quantitative level of inhibition, the claim is indefinite as written. The defendants suggest that, because the only competition

[8] It is noteworthy that the Harlow Laboratory Manual also discloses a method "to test whether antibodies recognize *similar* sites on protein antigens." ED HARLOW & DAVID LANE, ANTIBODIES: A LABORATORY MANUAL 590 (Cold Spring Harbor Laboratory 1988) (emphasis added).

assay disclosed in the specification requires competition between A2 and cA2, and A2 and cA2 share the same variable region, then the level of inhibition between A2 and cA2 would be the same as an assay that measured inhibition of an antibody against itself. Contrary to such logic, however, the specification incorporates by reference strategies and techniques for determining whether antibodies competitively inhibit binding to an antigen. *See* HARLOW & LANE at 567, 569. As suggested by the Harlow reference, competitive inhibition is characterized by whether the level of inhibition continues to increase as more of the competing antibody is added. *Id*.

For all the above reasons, the court adopts the plaintiffs' construction.

The court defines "competitively inhibits binding of A2 (ATCC Accession No. PTA-7045) to human TNF-α" as **"competes with A2 (ATCC Accession No. PTA-7045) for binding to human TNF-α."**

D. "binds to a neutralizing epitope of human TNF-α in vivo with an affinity of at least 1 x 10^8 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis"

Claim term, phrase or clause	Centocor's Proposed Construction	Defendants' Proposed Construction
"binds to a neutralizing epitope of human TNF-α in vivo with an affinity of at least 1 x 108 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis"	"Results in a loss of biological activity when it binds to human TNF-α in vivo; and associates (binds) with human TNF-α with an affinity of at least 1 x 10^8 liter/mole as calculated using a method for data analysis known as a Scatchard analysis"	"Binding of the anti-TNFα antibody is to a 'neutralizing epitope' if binding results in a loss of biological activity associated with the human TNFα, and further binds to the epitope in the organism with an affinity of at least Ka=1x10^8 liter/mole as measured in the living organism using Scatchard Analysis."

Within the '775 patent, the above phrase appears in independent claims 1 and 13 and dependent claims 4, 5, and 6.

In construing the above phrase, the parties dispute whether the claim requires the affinity to be tested *in vitro* or *in vivo*. Affinity, in the context of the patent, can generally be described as the measure of the strength of the interaction between an antibody and an antigen. One of the

embodiments describes determining the affinity of an antibody for an antigen involving, for example, radioactive labeling of an antibody and subsequent calculation of an affinity constant, all conducted *in vitro*. '775 Patent, col. 49, ll. 5-21; *see* '775 Patent, col. 7, ll. 21-25; Figs. 10A, 10B. The defendants seek to literally interpret the claim language and require the analysis to be conducted *in vivo*. The portions of the specification that the defendants cite do not support such a literal construction; each portion discusses the neutralizing or inhibition effect of the anti-TNF-α antibody, not the affinity analysis. *See* col. 6, ll. 5-10; col. 13, ll. 21-26; col. 36, l. 65-col. 37, l. 5. Although a construction that would render the claim nonsensical may be appropriate in certain circumstances, in this case, the claim is susceptible to a reasonable construction. *See Chef Am., Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1374 (Fe. Cir. 2004). It is well known in the art that such analysis is conducted *in vitro*, and that the data correlates with the affinity *in vivo*.[9]

For these reasons, the court adopts the plaintiffs' proposed construction.

The court defines "binds to a neutralizing epitope of human TNF-α in vivo with an affinity of at least 1 x 108 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis" as **"results in a loss of biological activity when it binds to human TNF-α in vivo; and associates (binds) with human TNF-α with an affinity of at least 1 x 10^8 liter/mole as calculated using a method for data analysis known as a Scatchard analysis."**

E. "inhibits a pathological activity of human TNFα"

Claim term, phrase or clause	Centocor's Proposed Construction	Defendants' Proposed Construction
"inhibits a pathological activity of human TNFα"	"Inhibits a TNF-α-mediated biological activity associated with a clinical problem such as disease, infection and/or malignancy"	"Inhibits a biological activity such as cytotoxicity, inflammation, or other activity associated with human TNFα mediated disease or damage."

[9] Scatchard analysis often involves labeling an antibody with radioactive material.

This term appears in claim 11 of the '239 patent. The claim reads as follows:

> 11. The antibody or antigen-binding fragment of claim 9, wherein said binding of the antibody or antigen-binding fragment to human TNFα inhibits a pathological activity of human TNFα. '239 Patent, cl. 11 (emphasis added).

The defendants dispute only the inclusion of "clinical" in the plaintiffs' proposed construction. They argue that such limitation suggests that clinical testing, rather than *in vitro* testing, is required to show inhibitions of pathological activity of TNF-α. The defendants cite to a portion of the specification that discloses *in vitro* assays that show antibodies inhibiting cell death caused by TNF-α, concluding that such antibodies have therapeutic use for treating TNF-α-mediated pathologies. *See* '775 Patent, col. 50, l. 1-col. 51, l. 57.

The plaintiffs' proposed construction unnecessarily limits the inhibition of pathological activity to clinical problems, especially when the specification expressly allows for testing of inhibition through *in vitro* assays. The inclusion of "clinical" in the plaintiff's construction unnecessarily limits the claim scope.

Accordingly, the court construes the disputed phrase as follows:

"inhibits a TNF-α-mediated biological activity such as cytotoxicity or inflammation, or one associated with a clinical problem such as disease, infection and/or malignancy."

F. Agreed and Undisputed Terms

The parties originally disagreed as to the construction of "neutralizing epitope." In their response, however, the defendants indicate that they discern no appreciable difference between the two proposed constructions. Accordingly, the court adopts the plaintiffs' proposed construction.

The court defines "neutralizing epitope" as **"portion of TNF-α, which, when bound by an antibody, results in a loss of biological activity of TNF-α."**

During the claim construction hearing, the defendants agreed to adopt the plaintiffs' construction of "recombinant," "produced recombinantly," and a modified construction of "specificity" that includes both parties' proposed construction.

Accordingly, the court adopts the plaintiffs' construction of "recombinant" and "produced recombinantly."

The court defines "recombinant" as **"encoded by DNA made with recombinant DNA technology, e.g., encoded by a gene that was built by splicing DNA."**

The court defines "produced recombinantly" as **"produced in a recombinant host cell, e.g., produced from a source (organism or cell line, for example) that includes a gene that was built by splicing DNA."**

The court defines "specificity" as follows: **"property of antibodies which enables them to bind to a neutralizing epitope of human TNF-α and chimpanzee TNF-α, but not to human TNF-β or TNF-α of other nonhuman species."**

The parties agree on the construction of "high affinity."

The court defines "high affinity" as **"an affinity of at least 1 x 10^8 expressed as an association constant (Ka)."**

IV. Conclusion

The court adopts the constructions set forth in this opinion for the disputed terms of the patents. The parties are ordered that they may not refer, directly or indirectly, to each other's claim construction positions in the presence of the jury. Likewise, the parties are ordered to refrain from mentioning any portion of this opinion, other than the actual definitions adopted by the court, in the presence of the jury. Any reference to claim construction proceedings is limited to informing the jury of the definitions adopted by the court.

SIGNED this 6th day of April, 2009.

T. JOHN WARD
UNITED STATES DISTRICT JUDGE